

REPORT
ON THE
TREATMENT OF PLAGUE
WITH
YERSIN-ROUX SERUM
AT THE
MARATHA HOSPITAL
DURING 1905,

BY
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Report on the Treatment of Plague with Yersin-Roux Serum at the Maratha Hospital during 1905.

The Serum Treatment among White Races.

Although the serum, discovered by Yersin, for the cure of plague has been in existence since 1896-97, it has not had a systematic trial on a sufficiently large scale in India up to within the last year or two. It has been used, however, at Glasgow, Oporto, Cape Town, Natal, Mauritius, Brisbane, etc., with results considered satisfactory by the observers. All these observations were confined to the white races only, who, as is well known, exhibit greater resistance to, and consequent lesser mortality from plague than the natives of India. Moreover, they resort to early treatment, a desideratum that is conspicuous by its general absence in this country. The rate of mortality for instance, at Brisbane,* during 1902, was found to be as low as 13·8 per cent. in 65 patients treated with the serum.

Previous Observations in India, 1897.

2. On the other hand, the observations of Yersin, Simond Mason and the German Plague Commission† in India during 1897, whilst indicating a large reduction in the mortality rate, fell far short of the above results. They treated 273 patients at Bombay, Cutch Mandvi, Karad and Karachi during the first epidemic of plague, when the full virulence of the disease had not yet declared itself. The results indicated that out of the above number, 144 patients died and 129 recovered, giving a mortality rate of 52·7 per cent. They found that the mortality rate could be considerably lowered if the patients could be treated on the first day of illness. In 39 patients treated on the first day, they had a mortality rate of only 33·3 per cent., that is about 20 per cent. lower than their average. The extremely favourable influence of the serum under such circumstances has been fully corroborated by other observers also.

Observations at the Plague Hospitals at Bombay, 1901-03.

3. During the four subsequent epidemics, the Yersin Serum—now improved and modified by Professor Roux of the Institut Pasteur of Paris—scarcely received any attention on account of the extended use of Lustig's serum, locally prepared. A few isolated observations were conducted by Dr. A. Mayr and myself at the Arthur Road, Modikhana and Maratha Hospitals during

* Report of 117 cases of Plague in Sporadic Form in Brisbane by Dr. Halford.

† Report of the Indian Plague Commission, 1902.

1901-03, numbering in all 77 cases, of whom 58 died and 19 recovered, giving a mortality rate of 75·3 per cent. ; 66 of the above number were treated on the alternate system, and the serum cases exhibited a difference of 7·4 per cent. in their favour as compared with a similar number of cases treated by ordinary methods :—

| | No. | Died. | Recovered. | Mortality per cent. |
|--|-----|-------|------------|---------------------|
| Control Cases | 66 | 58 | 8 | 87·7 |
| Serum Cases | 66 | 53 | 13 | 80·3 |
| Difference in favour of Serum Cases | | | | 7·4 |

Observations at the Maratha Hospital during 1904.

4. The next series of observations was conducted at the Maratha Hospital during the epidemic of 1904 by Dr. West, on behalf of the late Director-in-Chief of the Plague Research Laboratory, under my general supervision. The alternate system was adopted, and 80 patients were treated with the following results :—

| | No. | Died. | Recovered. | Mortality rate per cent. |
|--|-----|-------|------------|--------------------------|
| Control Cases | 80 | 50 | 30 | 62·5 |
| Serum Cases | 80 | 55 | 25 | 68·7 |
| Difference in favour of the Control Group | | | | 6·2 |

The serum group not only showed no advantage over the control, but it gave a higher mortality rate by 6·2 per cent. It is not necessary here to go into the causes of the above unfavourable results, so opposed to the general and accepted view of the utility as the serum treatment, as I have already referred to them in the report of the Maratha Hospital for the last year. This much however may be said, that the alternate system, as hitherto applied, is not scientific and is not the system best calculated to bring out satisfactory results in a disease so complicated as plague. And further, that the instance of observations on similar lines in diphtheria, so often cited in its favour, is inapplicable to plague, where numerous factors not existing in the former affection greatly enhance the difficulties incidental to the action of the serum on the human body, and where radical differences in the nature of the two diseases and in that of their infecting organisms are so patent.

Observations at the Maratha Hospital during 1905.

5. In view of the above unsatisfactory results, a further trial of the serum on a better system appeared to be necessary and I addressed Dr. Turner, the Executive Health Officer, to that effect, so as to obtain a large quantity of serum for use during the epidemic of 1905.

On his recommendation, Mr. Harvey, the late Municipal Commissioner, who always evinced a keen interest in serum treatment, sanctioned its purchase. About 95 litres of serum were received from the Institut Pasteur of Paris towards the end of February 1905, and observations were commenced with it from 1st March. Instead of wasting the serum on patients whom we knew from past experience to be not amenable to *any* treatment after a certain stage in the disease had been reached, *i.e.* those actually in the moribund condition, or exhibiting symptoms of grave cardio-vascular paresis, and consequent impending heart-failure, it was determined to apply it to such cases only in the *acute stage*, whose circulatory system had not been so gravely affected and who had a fair, but by no means always, a favourable pulse. All semi-convalescent and convalescent patients were excluded from the serum treatment for obvious reasons. In order to allow of comparison between the cases treated with and without serum, the use of the serum was suspended during certain intervals, and as the full virulence of the disease lasted during March, April and May, it was not difficult to secure a sufficient number of comparative observations.

Four Series of Observations.

6. The observations were thus divided into 4 series :—

*First Series :—*The first series was commenced on 1st March and lasted till 19th idem. It comprised 102 patients; 89 patients were rejected as unfit for the treatment in accordance with the plan above sketched out. From the 19th to 31st March the serum treatment was suspended for purposes of comparison.

*Second Series :—*The second series lasted from 1st to 10th April and comprised 53 cases; 64 cases were rejected as unfit for serum treatment. From the 10th to 20th April, the serum was again suspended for comparison.

*Third Series :—*The third series comprising 51 cases was commenced on 21st April, and lasted till 4th May; 46 cases were rejected as unfit for serum treatment. The stock of serum having become practically exhausted no further observations could be made from 5th May.

*Fourth Series :—*The fourth series included 16 patients, treated during January and the latter end of May, and some in June and July; several patients provided the serum at their own cost.

The System of Serum Treatment.

7. (a) In the first series, each patient received 2 subcutaneous injections of serum per day, one morning and evening. The serum was injected as close to the proximity of the buboes as possible. The maximum quantity injected per day varied from 150 to 200 c. c.

(b) In the second series, only one injection was given daily in the morning, the maximum quantity injected varied from 50 to 100 c. c.

(c) Whilst the above observations were going on, Prof. C. J. Martin of the new Plague Research Commission visited the Maratha Hospital, and discussed with me the various systems of treatment. His estimate of the value of the alternate system, as hitherto applied, was in accord with what I have said above, and whilst approving of the method already adopted in the first and second series, he proposed that in order to arrive at a fixed numerical demonstration of the value of the serum treatment, some system of simultaneous comparative observations should be instituted. He suggested, that after the rejection of the unfit, as in the first and second series, every alternate case should be treated with the serum, so that those left untreated would be the controls for purposes of comparison. It was this system of what may be called "Rational Alteration," that was adopted in the third series. It comprised 102 cases fit for treatment, 51 of whom were treated with the serum, and 51 left as controls. 46 cases were rejected as unfit for serum treatment. Only one injection of serum was given every morning, and the daily average came to 50 to 100 c.c.

(d) In the fourth series there was no elimination of the unfit, as most of the patients supplied their own serum and had to be injected. Two injections per day were given as in the first series. It comprised 16 patients only.

The Results of Treatment.

8. The following statement shows the results of the serum treatment in the four series:—

| | No. | Died. | Recovered. | Mortality per cent. |
|--------------------|-----|-------|------------|---------------------|
| First Series... .. | 102 | 61 | 41 | 59.8 |
| Second „ | 53 | 31 | 22 | 58.4 |
| Third „ | 51 | 37 | 14 | 72.5 |
| Fourth „ | 16 | 9 | 7 | 56.2 |
| Total..... | 222 | 138 | 84 | 62.1 |

The results of the third series with the controls can be expressed as under :—

| | No. | Died. | Recovered. | Mortality per cent. |
|--|-----|-------|------------|---------------------|
| Control Group | 51 | 42 | 9 | 82.3 |
| Serum Group | 51 | 37 | 14 | 72.5 |
| Difference in favour of the Serum Group | | | | 9.8 |

10. What value the above results represent can be determined by analysing the same in three different directions :—

Firstly.—By comparing the results of the cases treated with and without the serum.

Secondly.—By comparing the third series of the serum and control cases.

Thirdly.—By adding together the serum and rejected cases and comparing their mortality rate with that of the non-serum cases, in order to find out whether there was any, and if so, what influence on the reduction of mortality rate *on the whole* in the former group.

(a) Before entering into the details of comparison, it would be advantageous to note the virulence of the epidemic in January and February, before it reached its fastigium, which was more prolonged than usual and so far as clinical observations went, extended right up to the end of May. During these two months 333 acute cases of plague were admitted at the Maratha Hospital and the results of ordinary drug treatment were as under :—

| 1905. | No. | Died. | Recovered. | Mortality per cent. |
|-----------------|-----|-------|------------|---------------------|
| January | 112 | 86 | 26 | 76.8 |
| February | 221 | 176 | 45 | 79.6 |
| Total | 333 | 262 | 71 | 78.6 |

The mortality rate during February was over 3 per cent. higher than in January, and as is usual in all epidemics the tendency would have been to go higher still as the epidemic

advanced. That is corroborated by the following statement of non-serum cases, during the intervals when the use of serum was suspended :—

| 1905. | No. | Died. | Recovered. | Mortality. per cent. |
|------------------------|-----|-------|------------|-------------------------|
| March 19th-31st | 108 | 85 | 23 | 78.7 |
| April 10th-21st | 131 | 116 | 15 | 88.5 |
| May 5th-31st | 167 | 137 | 30 | 82.0 |
| Total ... | 406 | 338 | 68 | 83.2 |

It is evident from the above that the three periods during which, the serum treatment was applied (1st to 19th March; 1st to 10th April and 21st April to 5th May) coincided with the period of the maximum virulence of the epidemic, and that whilst the mortality rate in the non-serum cases was 83.2 per cent. it was 62.1 per cent in the serum group. There was thus an advantage of over 21 per cent. in favour of the serum cases. On the other hand, it will be argued that the above comparison is not fair, inasmuch as whilst the non-serum group comprised *all* the acute cases, there was considerable elimination of moribund and semi-moribund acute cases in the serum group on account of the system of rejection adopted, and hence the method of comparison was to that extent favourable to the serum cases. That is a perfectly valid objection which will be discussed further on.

(b) The second method of comparison between the serum and control cases in the third series, indicates that in 51 cases treated on either side, the serum cases showed an advantage of about 10 per cent. in their favour. This may be taken to be the expression of the numerical demonstration of the value of the serum treatment in *hospital practice*. And the fact that it should almost coincide with the results of the alternate system of treatment carried out in 968 patients at the Arthur Road Hospital during 1899-1900 with Lustig's serum, indicates that neither of these results could have been accidental or fortuitous as has been alleged with reference to the observations with Lustig's serum. With the alternate system, the Lustig's serum cases showed an advantage of 11.5 per cent. over the control group.

(c) The third method of comparison fully meets the objection raised in the above para and it will be interesting to note whether the mortality was reduced *on the whole*, if the serum, control and

rejected cases, were amalgamated and compared with the cases treated without the serum as under:—

| (a) Serum (b) Control and (c) Rejected cases. | | | | Cases treated without Serum. | | | |
|--|-------|------------|------------------------|------------------------------|-------|------------|------------------------|
| No. | Died. | Recovered. | Mortality per cent. | No. | Died. | Recovered. | Mortality per cent. |
| (a) 222 | 138 | 84 | 62.1 | | | | |
| (b) 51 | 42 | 9 | 82.3 | 406 | 338 | 68 | 83.2 |
| (c) 199 | 189 | 10 | 94.9 | | | | |
| 472 | 369 | 103 | 78.1 | 406 | 338 | 68 | 83.2 |

Here again we find that in spite of combining the serum group with the control and rejected cases, the results are still favourable to serum treatment. Although only 222 patients were treated with the serum in a total of 472, the mortality rate on the whole is lower by 5 per cent. than in 406 cases treated without the serum. It may be noted that out of 199 patients rejected as unfit for serum treatment, only 10 recovered under the ordinary drug treatment.

On the whole, therefore, there can be no doubt that there was distinct gain under the serum treatment, and that more lives were saved than under the ordinary treatment.

11. What influence the nature of the epidemic had on the results of the serum treatment is a question of importance and so also is another, viz :—Whether the system of treatment adopted favoured or acted adversely to the results. That the character of the last epidemic did not in any way favourably influence the results of the serum treatment is indicated by the comparative tables of mortality rates given in a former para.

Secondly, if the graver manifestations and complications of plague in the serum and non-serum groups be compared, the conclusion we arrive at is that in spite of the system of rejection adopted, the serum patients were in no way favoured, as they actually showed a greater preponderance of such complications.

At the same time it should be noted that the serum group showed proportionately more recoveries from the same than the non-serum group :—

| Complications. | 222 Serum cases. | | | 656 Control, Rejected and non-Serum Cases. | | |
|------------------------------|------------------|-------------------------------------|------------|--|-------------------------------------|------------|
| | No. | Per Cent- age to total cases. | Recovered. | No. | Per Cent- age to total cases. | Recovered. |
| Secondary Pneumonia | 15 | 6.7 | 4 | 25 | 3.8 | 1 |
| Coffee ground vomit- ing. | 10 | 4.5 | 1 | 23 | 3.5 | |
| Hæmatemesis... .. | 1 | 0.4 | | 5 | 0.7 | |
| Hæmaturia | 10 | 4.5 | 6 | 10 | 1.5 | 4 |
| Marasmus | 22 | 9.9 | | 26 | 3.9 | 1 |
| Meningitis | 6 | 2.7 | | 6 | 0.9 | |
| Tympanites (grave) ... | 10 | 4.5 | 6 | 2 | 0.3 | |

The foregoing statement denotes that in the serum cases the grave complications preponderated. The disproportion in the rate of marasmus between the groups is indeed striking as it was nearly three times as high in the serum cases.

The Serum Treatment in Private Practice.

12. This report would be incomplete without reference to the large amount of work done with the serum in private practice during the epidemic of 1905, especially as it would enable us to compare the results with our hospital experience. The medical gentlemen who had adopted the serum treatment were addressed on the subject and four of them very kindly furnished the necessary particulars for the purpose of this report. I beg to express my cordial thanks to them for their co-operation. It appears that 106 patients have been treated in private practice with the following results:—

| Observers. | No. | Died. | Recovered. | Morta- lity per cent. | Average amount of Serum in- jected per patient. | Average amount of serum per recovery. |
|---|-----|-------|------------|--------------------------------|---|--|
| Dr. B. Pais | 54 | 27 | 27 | 50.0 | 130 c.c. | 200 c.c. |
| Drs. C. Fernandes and M. A. de Heredia ... | 31 | 12 | 19 | 38.7 | 230 " | 240 " |
| Dr. Chokey (in con- sultation). | 15 | 4 | 11 | 26.6 | 475 " | 500 " |
| Dr. A. Mayr | 6 | 3 | 3 | 50.0 | 550 " | 540 " |
| Total | 106 | 46 | 60 | 43.3 | | |

Only one doctor declined to supply the particulars, although he said he had treated very few cases.

The above results were superior to those obtained in hospital practice, as the mortality rate was 43·3 per cent. as compared with 62·1 per cent. in hospital cases. Satisfactory as the above results are, it must be noted that the serum was not always applied under the best or even favourable circumstances, inasmuch as about half the number of patients treated were poor Goanese, who, whether living in their clubs or shops could hardly afford, and had practically no adequate nursing or even proper care. In spite of such disadvantages, their average hospital mortality rate was lowered by more than 15 per cent. The better class of Hindoo and Parsee patients have to some extent counterbalanced this. The results in private practice with this serum also coincide with those obtained with Lustig's Serum :—

| | No. | Died. | Recovered. | Mortality per cent. |
|--------------------------|-----|-------|------------|---------------------|
| Lustig's Serum | 130 | 58 | 72 | 44·6 |
| Yersin-Roux Serum | 106 | 46 | 60 | 43·3 |

The results are practically identical in both instances.

As regards the class of patients treated in private practice more than half the patients were Goanese, and about one-fourth Hindoos. Amongst Parsees, only 11 cases were treated as against 60 with Lustig's Serum. A considerable reduction in the average mortality rate in all communities is however noticeable. The following table compares the results of treatment in hospital and private practice in the different races :—

| | Hospital Patients. | | | | Private Patients. | | | |
|------------------------------------|--------------------|-------|------------|---------------------|-------------------|-------|------------|---------------------|
| | Number. | Died. | Recovered. | Mortality per cent. | Number. | Died. | Recovered. | Mortality per cent. |
| Hindoos | 152 | 106 | 46 | 69·7 | 28 | 11 | 17 | 39·2 |
| Christians (mostly Goanese) | 34 | 12 | 22 | 35·3 | 59 | 29 | 30 | 49·1 |
| Mahomedans | 26 | 15 | 11 | 57·6 | 6 | 2 | 4 | 33·3 |
| Parsees | 10 | 5 | 5 | 50·0 | 11 | 3 | 8 | 27·2 |
| Chinese | ... | ... | ... | ... | 1 | ... | 1 | 0·0 |
| Jew | ... | ... | ... | ... | 1 | 1 | ... | 100·0 |
| Total..... | 222 | 138 | 84 | 62·1 | 106 | 46 | 60 | 43·3 |

The private patients show a better recovery rate than the hospital patients in all classes except the Goanese ; that must be due chiefly to the better care and nursing obtainable in the hospital, which in a large proportion of cases they did not have at home. The difference between the two classes of Hindoo and Mahomedan patients is very striking being 30 and 24 per cent. respectively, owing to the vast differences in the stamina and social position of the patients, and early treatment. Those treated at home belonged to a better class, whereas those at the hospital were drawn from the lower and lowest strata of Hindoo and Mahomedan communities. As regards Parsees, the number is too limited for comparison, but the combined result of hospital and private cases, showing a mortality rate of only 38·0 cannot be ignored.

Bacteriolysis.

13. In a previous report* the theoretical considerations involved in the practical application of serumtherapy and the action of various serums have been fully discussed in the light of the recent investigations of Pfeiffer, Metchnikoff, Bordet, Ehrlich, Morgenroth, Wassermann, Behring, Von Dungern, Bulloch, Wright and others. The various serums used in the treatment of plague are what are called, *bacteriolytic serums*, that is, that under certain specified conditions they are capable of disintegrating and dissolving the bodies of the bacilli. They require for their action, the presence of certain substances within the body of the patient called *Alexines* or *Complements* which under the stimulus of the infecting agent are elaborated in the blood, especially in the white blood corpuscles or leucocytes. And it is this combination of the active principle of the serum—called *immune body* or *amboceptor* with the *complements* that brings about bacteriolysis. The presence of both is absolutely necessary for the process ; either alone is useless. This disintegration of the bacilli liberate the toxins contained in their bodies, which have to be neutralised and eliminated from the system before complete recovery can take place. If the serums were also capable of combining with and neutralising these toxins, they would then be possessed of *anti-toxic* properties as well. But inasmuch as the various serums used for the treatment of plague are but feebly anti-toxic, it is probable that the system itself supplies the deficiency by producing anti-toxins, which within certain limits neutralise the toxins and prevent their combination with the tissue cells of the body. So long as the infection is moderate, the serums are able to cope with the resulting toxæmia. But experiments on animals have demonstrated that a certain degree of infection having been reached, it is of no consequence however how much serum is given ;—the result is the death of the animal. Such has also been our experience in man. In

* Report on the Treatment of Plague with Prof. Lustig's Serum during 1900-01 submitted to the Municipal Corporation for the City of Bombay. Also see The Treatment of Plague with Prof. Lustig's Serum, by the Author, 1903.

septicæmic, pneumonic and grave bubonic cases, massive doses of the serum, although they have prolonged life, have been incapable of curing the patient. It must therefore be clearly understood that there is a limit beyond which the antiplague serums cannot act. And even in grave infections just short of this, it is not always possible to bring round the patient, because the toxæmia produced by the resulting action of the serum, is so intense and so difficult of neutralization and rapid elimination. There supervenes a new phenomenon that is fatal to the patient, viz. the combination of the toxins with the nerve and other important tissue cells of the body producing grave changes in the system. This result is indeed to be deplored, but it is a fact that has to be recognised. Where nature acts independently of art—in those instances where plague patients recover without the aid of serums—the process of overcoming the infection is the same and both the substances requisite to bring about bacteriolysis are produced in the blood of the patient. But there too, whilst every plague bacillus in the body may be destroyed, the risk of toxæmia exists, but not to the same extent as where serums are used, because nature unaided is not able to disintegrate the bacilli, if the infection is grave and the patient usually dies before complete bacteriolysis can take place. This toxæmic condition has been clinically described as Plague Marasmus.

Plague Marasmus.

14. Plague Marasmus occurs in two forms, the acute and the sub-acute. It shows itself about the time the patient is getting apparently better—about the eight or tenth day. Considerable improvement in his general condition, the pulse and temperature almost normal, the bubo either small, hard, and getting gradually absorbed or just suppurating; and the body free from living plague germs, are the antecedent conditions. In the course of a day or so, or even during a single night, a sudden change is noticeable in the patient. The face becomes pinched and hollowed out from rapid wasting and shrinkage of the adipose and muscular tissues; the bones and prominences start out from the face; the eye-balls sink; the look becomes vacant and he lapses into a condition of semi-stupor from which he can be roused with difficulty. Speech becomes inaudible, and reduced to a whisper; the patient moans occasionally and does not like to be disturbed. The decubitus is dorsal. The pulse, a few hours before so hopeful, becomes thready, and the extremities cold. There is great prostration and general heavy condition of the limbs, which become almost leaden, and paresis of the muscles of deglutition may supervene making feeding difficult. Simultaneously with the above symptoms, the body becomes intensely icteric. The conjunctiva and nails, become yellow; the skin of the same hue, and all the excretions highly charged with bile. There is not much rise of temperature at first unless there exists at the same time some se-

condary infection or deep suppuration. The patient remains in this condition for a day or two and then the stupor becomes intensified, the pulse weaker and weaker, the wasting increasing considerably till the extremities and trunk are involved. The reflexes are abolished; glosso-labio-pharyngeal paralysis sets in and so also polyneuritis, if life is prolonged. The cornea becomes glazed, and either keratitis or panophthalmitis result. The decubitus may now become lateral with the knees drawn up, and the legs flexed over them. The temperature steadily rises and when death supervenes within six to eight days from the onset of the above symptoms, it may be as high as 106° - 107° . All these symptoms indicate profound intoxication of the system. In one of the foregoing tables the proportion of marasmus in patients treated with the serum has been given as about three times as much as in those without, and that is but a logical sequence of the use of the serum. For whilst nature unaided can produce disintegration of the bacilli in only a few of the grave cases, serum must do so in a large proportion.

The same phenomena are observed in cases not treated with the serum, but as stated above in lesser proportion and they supervene if a large or even moderately sized bubo gets rapidly absorbed and disappears within a day or two, thus surcharging the system with the liberated toxins. The same train of events follow as in the serum cases, and the fatality is always the same. In the 222 serum cases, 17 cases of acute marasmus were observed, as against 13 in 656 non-serum cases. Not one of them however recovered.

15. In the sub-acute form, all the above symptoms exist but they develop very gradually after about a fortnight's illness, and last much longer. Whilst in the acute form, the patient dies within the third week of illness, the sub-acute form may extend to over six, eight or even ten weeks. The condition of the patient is then extremely pitiable. The wasting progresses over the whole body, all the flesh practically melts away, and the patient is reduced to a skeleton. Trophic changes in the eye supervene and sight may be totally lost through panophthalmitis; as also in the bones and joints which swell: ulcers and bed-sores form in spite of every care and attention; the power of speech and deglutition may be completely lost. The reflexes are abolished; the urine and faeces are voided involuntarily; the saliva dribbles from the angles of the mouth, and as the secretions of the throat and lungs cannot be expelled, they accumulate in the throat and almost choke the patient. Glosso-labio pharyngeal paralysis and polyneuritis supervene. The muscles become contracted, and every movement becomes painful. The patient lies doubled up, a dull, shapeless and wasted being; there is no adequate response to even strong stimuli and all that he can express in reply to calls is a groan or whine, unintelligible

and scarcely human. At times, there is a vacant stare in the eye, but there is no recognition. He can hardly be said to live, but exists, until merciful nature comes to his aid and ends the misery. Here and there a recovery may be possible, but almost all such cases end in death. Convalescence is extremely prolonged, and it may take four to six months before the patient can move about. In other instances, the after-effects last for years, and the patient is never himself again as defects in speech and power of mobility become almost permanent. In the serum group 5 such cases were observed, and in the non-serum 13 of whom only one recovered.

Between these two forms of marasmus, there exist a few cases who may be said to be on the borderland of marasmus. They appear to be about to merge into it, when improvement sets in and they recover, though recovery is tardy. In such instances the toxæmic condition is just enough for the system to cope with and no more.

It will be observed that out of 48 cases of marasmus, but one recovered. The only way in which it would be possible to save such lives would be by the use of an *anti-toxic serum* to supplement the action of the *bacteriolytic serum* so as to completely antagonise the living virus, and neutralise the products of its disintegration. Such a serum is still a desideratum and until one is discovered or until both properties are combined in one serum, it cannot be said that the problem of successful serum-therapy in plague has been solved.

When is the Serum Most Effective?

16. The general consensus of workers in serum-therapy is that the earlier the serum is used, the more effective it is. In diphtheria, the mortality in cases treated on the first day of illness has been reduced to almost nil, after which it however rises, but quite out of proportion to the duration of illness. The same has been our experience in plague. When Lustig's serum was in use, the mortality rate in 26 cases treated on the first day in private practice was as low as 15·3 per cent., but in 34 cases treated on the second day it was as high as 58·8—that is, a difference of 24 hours, or even less in the use of serum enhanced the death rate nearly four times. The advantages therefore of early treatment, are so manifest that it is nothing short of criminal to delay or withhold the serum, even if a positive diagnosis be not made. One or two injections of serum not only do no harm, but should the patient be suffering from plague, cut short the disease. The results of early treatment are so satisfactory that if patients are treated on the first day of illness, the disease can be practically arrested and its normal duration of 8 to 10 days reduced by half or even less, and the patient declared out of danger by the fifth day, if not earlier. The whole course of the disease becomes thus modified: serious complications of the nervous and circulatory systems—so fatal in plague—are averted;

the temperature is rapidly controlled, the bubo becomes absorbed, and recovery is rapid. Although patients treated on the second day do not respond thus, even then, they are better off than those treated on the third day or later. It has to be recognized, however, that the fatality is out of all proportion to the difference in the period of treatment. It is not possible to influence the course of the disease in patients treated on or after the third day, although more do recover. But on the whole, convalescence is more readily established, and recovery is also proportionately more rapid. The subjoined comparative statement confirms the above conclusions. The proportion of early cases is greater in private practice as is but natural, for very few early cases are brought to the hospital, unless the patients are very ill on the first-day of illness. The proportion of first day cases was 22·5 per cent. in the observations of 1897. The proportion in private practice in 1905 was 35·8 per cent. as against 5·4 per cent only in hospital cases :—

| Duration of Illness. | 1897. | | 1905. | | 1904-05. | |
|----------------------|--|---------------------|--------------------------|---------------------|-------------------------------|---------------------|
| | Yersin, Simond and The German Plague Commission. | | Maratha Plague Hospital. | | Patients in Private Practice. | |
| | No. | Mortality per cent. | No. | Mortality per cent. | No. | Mortality per cent. |
| 1st Day | 39 | 33·3 | 12 | 66·6 | 38 | 34·2 |
| 2nd „ | 71 | 52·1 | 69 | 60·8 | 24 | 58·3 |
| 3rd „ | 42 | 47·6 | 77 | 68·8 | 27 | 44·4 |
| 4th „ | 16 | 68·7 | 35 | 45·7 | 10 | 40·0 |
| 5th „ | 4 | 75·0 | 19 | 63·1 | 4 | 50·0 |
| 6th „ | 1 | 100·0 | 7 | 57·1 | 2 | 50·0 |
| 7th „ | ... | ... | 3 | 100·0 | 1 | ... |
| Total..... | 173 | 49·1 | 222 | 62·1 | 106 | 43·3 |

From the foregoing statement it will be observed that the mortality rate after the first day does not ascend in a regular scale and taking each series independantly the results do not appear to be consistent. The first-day hospital cases show a very high rate, whereas in the first and third series the rate is the lowest. On the second day only the hospital cases have a lesser rate than the above and so on. Such apparent discrepancies it is not possible to reduce to strict mathematical proportion as so

much depends upon the distribution of patients and their condition at the time of treatment. If however, we total up all the three series, we notice greater regularity in results :—

| Duration of Illness. | | | | Number. | Mortality per cent. | |
|----------------------|-----|-----|-----|---------|---------------------|--|
| 1st day | ... | ... | ... | 89 | 38.2 | |
| 2nd " | ... | ... | ... | 164 | 56.7 | |
| 3rd " | ... | ... | ... | 146 | 58.2 | |
| 4th " | ... | ... | ... | 61 | 50.8 | |
| 5th " | ... | ... | ... | 27 | 62.9 | |
| 6th " | ... | ... | ... | 10 | 60.0 | |
| 7th " | ... | ... | ... | 4 | 75.0 | |
| Total ... | | | | 501 | 53.6 | |

The mortality rate is lowest on the first day, and thereafter it increases according to the duration of illness until the fifth day, the fourth day excepted—when with fewer cases it is less than on the second day by nearly 6 per cent. It is rather curious that the same results should have been noted with Lustig's serum in the series of 480 cases treated on the alternate system. The ratio of mortality on the fourth day was also found to be about 9 per cent. lower than on the second day. That may be due, partly to the smaller number treated on the fourth day, and partly to the most serious cases having died off before the period. Such discrepancies are not always capable of satisfactory explanation in regard to plague.

Apart, however, from the better recovery rate under the serum treatment, there is early convalescence also. Two causes contribute to it, viz :—Fewer complications during convalescence and lesser suppuration of the buboes. There is almost uninterrupted recovery when buboes do not suppurate; if they do, the proportion is much less than in cases treated without serum. Among the 84 recoveries in the hospital, the buboes did not suppurate in 40 patients that is in 47 per cent. whereas the ratio is about 10 per cent. only in those under ordinary drug treatment.

Dosage of the Serum.

17. Much depends upon the early and free use of the serum. In patients injected on the first day or within a few hours of the onset of the symptoms, one injection of 100 c. c. followed by another after 6 to 8 hours, and then, if necessary, by a third, after a similar interval, would cut short the attack, if the case be not malignant or septicæmic. Thereafter one or two small injections of 20 to 50 c. c. may

be given as a matter of precaution. Abrupt stoppage of the serum under any circumstances is not safe, inasmuch as, should any poison remain unneutralised, it gets a fresh impetus to develop, and that too, to such a great extent in some instances, as to lead to serious results. It is possible however, that with mild cases, a smaller amount might suffice, but as it is practically impossible to determine the virulence of a plague case at the outset, it is preferable to err on the right side, and to use a little more, rather than a little less serum. So long as we know that an excess of serum does no harm—and there is nothing to show to the contrary—it is false economy—to the detriment of the patient, to stint it. The same procedure may be adopted in cases coming under treatment on the second day. On and after the third day, injections repeated with this frequency have not been of much use, as the time for cutting short the disease has already passed. The number of injections required in a particular case cannot be previously determined inasmuch as individual circumstances have to be considered, and the progress of the patient carefully watched. But whenever the evening temperature is found to be lower than the morning, it is a favourable indication, and the dose of the serum can be safely reduced for the evening injection or for the following morning. The following table compares the results of treatment according to the number of injections and the quantity injected :—

| Series. | No. of Cases. | Average No. of injections per patient. | Average No. of injections per recovered patient. | Average quantity of serum injected per patient. | Average quantity of serum injected per recovered patient. | Mortality per cent. |
|--------------------------------|---------------|--|--|---|---|---------------------|
| I (2 injections per day) ... | 102 | 9 | 12 | 590 c.c. | 660 c.c. | 59.8 |
| II (one injection) ... | 53 | 5 | 6 | 360 c.c. | 390 c.c. | 58.4 |
| III (Do. alternate system) ... | 51 | 5 | 6 | 350 c.c. | 360 c.c. | 72.5 |
| IV (2 injections) ... | 16 | 9 | 10 | 560 c.c. | 560 c.c. | 56.2 |
| Private Cases... | 106 | ... | ... | 130 to 550 c.c. | 200 to 400 c.c. | 43.3 |

Whilst in the first and fourth series two injections were given daily, only one was administered in the second and third. There is not much difference between the results of the first, second and fourth series, although the quantity of serum varied so greatly, but in the third series the mortality rate was much higher. This result does not appear satisfactory, but it is to be attributed rather to the greater virulence of the cases treated, than to any paucity of the serum, as the mortality rate at that period of the epidemic was 88.5 per cent. in the non-treated cases.

Specific rules for the frequency of injections and dosage are not applicable under all circumstances but the following directions, according to the duration of illness would offer the best chances of good result :—

Cases Treated on the First Day :—One injection of 100 c. c., followed by a second one of 100 c. c. after six to eight hours, and then if necessary, by a third of 100 c. c. after the same interval. Subsequently 2 more injections, one every morning of 20 to 50 c.c.

Cases Treated on the Second Day :—As above, or one injection of 100 c. c., to be followed by another of 100 c. c. after 8 to 10 hours, thereafter three to four injections in doses gradually reduced e. g. 80 c. c., 60 c. c., 40 c. c., or 20 c. c.

Cases Treated on the Third Day and After :—The same procedure as on the second day ; cases may be given two or only one injection daily thus :—(1) 100 c. c. (2) 100 c. c., (3) 80 to 100 c. c. (4) 80 c. c. (5) 60 c. c. (6) 40 c. c. and (7) 20 c. c.

Medicinal Treatment.

18. All the patients, whether treated with or without the serum received the same medicinal treatment, varied according to their nature, gravity and complications. No alcohol was administered under any circumstances. Fever was controlled by ice on the head, sponging or wet-pack. No antipyretics, local or general, were used. Cardiac failure was treated by Adrenalin Chloride. Solution (1-1000) and by the usual combination of Sparteine, Strychnine and Atropine.*

Locally, cold compresses over the bubo and seat of injections. Complications were treated on general principles.

After-effects of the Serum Treatment.

19. A close similarity exists between the after-effects of diphtheria antitoxin as described by Dr. Rolleston† and those observed after the use of anti-plague serum. He mentions rashes, joint pains, abscesses and hyperidrosis (profuse secretion of perspiration) ; and they all appear after injections of anti-plague serum with varying frequencies :—

(a) *Rashes* :—Three types of rashes or erythema have been observed ; the most common being circinate erythema, next in order scarlatiniform erythema, and the least frequent, the urticarial type. Circinate erythema is the most common and spreads outwards in all directions from the seat of punctures, covering well defined areas with marked circinate margins which are deeper in colour, than the diffuse erythema, they surround. It does not occur on parts of the body free from punctures of injections. A slight rise of temperature

* Cardiac Failure in Plague and its Treatment by the Author—Indian Medical Gazette April 1905.

† The Practitioner, May 1905.

generally accompanies it, but there is no systemic disturbance. Local irritation from pruritus causes annoyance which subsides within three or four days under cold compresses of boric acid.

Scarlatiniform erythema, more often general than local, comes next in order, but a long way behind. There is considerable systemic reaction, the temperature is raised, and thick eruption like that of a severe attack of scarlatina or measles develops. It is rather faint at first, but becomes gradually intensified. There is intense pruritus and it leads to restlessness and insomnia requiring the use of sedatives and even narcotics. Although the sudden change in the condition of the patient looks alarming, there is no cause for anxiety as the erythema gradually fades away in the course of four to six days.

Urticarial rashes are extremely rare; they are localised to the areas surrounding the seat of punctures or to the limbs. In my own case, wheals upon wheals with considerable oedema surrounding them appeared on both the upper extremities, as the injections had been given in the axilla and on the arm. They disappeared at one spot, on the application of ice, and reappeared at another within a few minutes. There was no constitutional disturbance and no rise of temperature, but intense pruritus which relieved by the application of ice. The eruption lasted for about 2 days only and then disappeared.

The rashes appear within one week of the injection of the serum and are of varying degrees of intensity. Hardly any patient escapes, and in all those cases who recovered under the serum treatment they were recorded. It is indeed curious that the rashes as well as the joint pains should affect those classes of people more who usually take meat than the strict vegetarians. Boric acid (dry or in compresses) and ice, generally allay the pruritus. Rolleston recommends Menthol, 1 drachm to Paraffin Alb. Mollé 1 ounce.

(b) *Joint Pains*.—Joint pains generally develop after the subsidence of rashes. There is effusion and swelling of the joints with intense pain, fever and difficult mobility. All the joints are not simultaneously affected, but by turns; after pain and swelling have subsided in one joint or set of joints, they appear in another and then in a third until practically hardly any principal joints of the body escape. The degree of pain and the number of joints affected bear no relation to the amount of serum injected. In my own case, for instance, although only 400 c. c. was injected, the joints were affected on both sides in the following order:—Phalangeal, metacarpal and wrist joints, then the elbow; the shoulder joints escaped although the serum was injected so near to them; then the metatarsal tarsal and ankle joints, followed by the knee, and lastly the temporo-maxillary joint on one side. Only one such case where so many joints were attacked, has come under my observation. The wrist and elbow or ankle and

knee are the joints usually affected. Joint pains occur in about 25 per cent. of those that recover under the serum treatment, and though not dangerous to life, cause much pain and misery by preventing sleep and retarding convalescence. They are however amenable to treatment, and leave no after-effects. Local applications of glycerine and belladonna, methyl-salicylate, mesotan or betul-ol and internally an alkaline mixture with or without salts of salicylic acid or aspirin are the means to control it. Pains in muscles and fascia are infrequent; they aggravate the joint pains; movement becomes extremely painful and practical immobility of the limbs may temporarily result.

(c) *Abscesses*:—Dr. Rolleston holds that abscesses after serum injections are due to discreditable lack of asepsis. In hospital practice, however, dealing with not overclean native patients, it is so difficult to prevent them. In spite of aseptic serum, aseptic instruments and as thorough a cleansing of the skin as is possible, abscesses do occur. It is practically impossible to render the skin thoroughly aseptic in many cases, and the more so if the skins are tough and horny. Oft times gaseous abscesses form which if incised early and appropriately treated do not give rise to any difficulty. The abscesses give no trouble in healing which is fairly rapid. They occur at varying periods after injection, but generally within three weeks. No infection with the bacillus *ærogenes capsulatus* has been noticed among the cases treated.

(d) *Hyperidrosis*:—Profuse secretion of perspiration has been noticed after intravenous injection, and so also coryza with excessive nasal secretion, and copious lachrymation. With subcutaneous injections, however, such is not the case, although during convalescence in some patients it is to be occasionally met with. With increasing strength, it gradually disappears.

Concluding Remarks.

20. A careful and impartial survey of the whole field of serum therapy in plague, having constantly in view the limitations imposed by the nature of the affection, must perforce lead to but one conviction only, viz., that it is the only treatment capable of saving a greater proportion of lives in a certain class of patients. That it cannot favourably influence all types of plague, or even the malignant forms of bubonic plague must be recognised. As also the fact, that in *hospital practice*, where half the number of admissions are advanced too far for any beneficial influence, it must be of comparatively limited value. In every case of plague, there is constant disintegration and reproduction of the plague bacilli. Should the system be not capable of producing enough antitoxin to neutralise the toxins liberated by the disintegration, they combine with the tissue cells, a combination that is fatal to the individual. Greater success is possible only in those instances,

where such combination could be forestalled and that can only happen where early treatment is resorted to. That unfortunately is not possible in hospital patients. And again the great disparity between the results of treatment on the first as compared with those of the second day, should not be overlooked, indicating as they do the extreme gravity of withholding the serum even for a few hours. Under such circumstances, is it to be wondered at that in hospital practice, we have not been able to do more than to save about 10 to 20 more lives out of every 100, by the use of the serum? This result, be it remembered, is obtained in a disease that carries away about 84 people on an average out of every 100 attacked. From my long and intimate connection with plague, and its serum-therapy I am inclined to conclude that, for the present at least, the above must be considered to be the limit of our success. It has been impressed upon us, that were the serum used intravenously in preference to the subdural method, the results would be infinitely better. No doubt they would be were the circumstances favourable for its general adoption, and the material with which we have to deal, different. So long, however, as we have to work under conditions as hitherto obtainable, I do not think, better results are possible unless, indeed, it be that we obtain a serum combining both anti-toxic and anti-bactericidal properties. Then, perhaps, we could save a few more lives. To expect miraculous cures or even brilliant results, in a disease like plague is simply futile, and hardly in accord with our knowledge and experience, as well as our successes and failures, in the treatment of other grave infections.

21. The whole aspect of plague-serum-therapy, however, alters when applied under different, and in most cases, more favourable circumstances—that is in private practice. Here the patients belong to a better class of society, are better housed and better fed. They come under observation early, and unless there is gross carelessness or the symptoms marked, plague is recognised early and treated equally early. That the disease does not become altered, or its characteristics change, because the patient happens to be in a better social position is demonstrated by the great disparity between the results of the first day as compared with those of the second day treatment and once again it emphasises the cardinal fact that if good results are to be obtained from serum-therapy the patients must be treated on the first day of illness.

I consider the result obtained in private practice extremely satisfactory. They are capable of further improvement, if one could sufficiently impress upon the people, that it is only by treatment on the first day, that the patient has the best chance of getting over the disease. That time and education are in its favour is shown by the greater use that is now being made of the serum, and the greater confidence of the people in its usefulness and efficacy.